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(54) Title: A SLOW RELEASE PHARMACEUTICAL COMPOSITION COMPRISING A MAGNESIUM OXYCHLORIDE CEMENT

(57) Abstract: The invention relates to slow release pharmaceutical compositions. More particularly it relates to the combination of hygroscopic solid, liquid or gaseous pharmaceutically active substances with solidifying materials of the type known as Sorel cement thereby to produce solid compositions which, when taken orally, has slow releasing properties in respect of the substance so incorporated into the composition.

A SLOW RELEASE PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION:

This invention relates to slow release pharmaceutical compositions. More particularly it relates to the combination of hygroscopic solid, liquid or gaseous pharmaceutically active substances with solidifying materials thereby to produce solid compositions which, when taken orally, has slow releasing properties in respect of the substance so incorporated into the composition.

BACKGROUND TO THE INVENTION:

It is known that magnesium chloride hexahydrate and L-carnitine base are both recommended dietary supplements for a variety of indications.

The main function of carnitine in the human body is to help in the transport of long chain fatty acids. These fatty acids are utilized inside cells to provide energy. This is a major source of muscular energy. Thus carnitine is used in health supplements to boost energy, prevent fatigue, and maintain the body. Carnitine also increases the use of fat as an energy source thus preventing fat buildup in the heart, liver, and muscles. By doing so carnitine reduces poor metabolism health problems like diabetes, high tri-glyceride blood levels, obesity, weak muscles, and heart disorders. Carnitine has the added

benefit that it increases the effects of the anti-oxidants vitamin E and vitamin C. Carnitine supplementation has become very popular and the most common supplemental forms include L-carnitine, DL-carnitine, and acetyl-L-carnitine.

The applicant considers the concomitant supplemental intake of magnesium and L-carnitine to be desirable in, and beneficial for a number of patient groups whose bodies are considered to be under extraordinary physiological demand, leading to the development of L-carnitine and magnesium deficiency. These groups include (a) women in general in view of their hormonal fluctuations, but in particular those women having demanding lifestyles resulting from workplace and household responsibilities; (b) school going children, and particularly those in puberty; (c) sports people, and in particular those participating in competitive sport for whom the regular supplementation of these products contribute to the reduction, or even the prevention of, lactic acid build up, and furthermore enables the body to produce ATP when needed; (d) the chronically ill or compromised such as, for example, patients suffering from AIDS and undergoing treatment with anti-viral medication where it is known that the ailment and/or the treatment leads to L-carnitine deficiency.

It is known that magnesium chloride hexahydrate and L-carnitine base are hygroscopic on their own. They are even more so when mixed together. It

has accordingly long been considered impossible to administrate them separately, let alone together in the most desirable dosage form, namely as a dry, solid preparation, e.g. in tablet, capsule or granule form. They are presently being administrated together as a liquid compound. This liquid formulation is not generally considered to be user friendly, and hence conducive to patient compliance, as it has an unpleasant taste and has to be diluted in other liquids.

OBJECTS OF THE INVENTION:

To address the above problems, the present invention proposes, and is based upon, the hitherto unknown utilization of a method which, although known as such as a method of solidifying magnesium chloride hexahydrate, has, as far as the applicant is aware, not yet been suggested for use in the manner proposed herein for the preparation of the slow- or sustained release preparations of any one of the wide range of pharmaceutically beneficial products, including, but not limited to L-carnitine, which may be incorporated into the solid composition as proposed by the present invention.

It is accordingly an object of the present invention to provide a solid, slow release dosage form of a pharmaceutically active substance or combination of substances, and specifically, though not exclusively, of a substance or combination of substances which is hygroscopic, or which is a liquid which

contains or is soluble in water, such as, for example, the compound L-carnitine, alcohol and nitrous oxide gas.

PRIOR ART TO THE INVENTION:

The aforementioned known method of converting magnesium chloride into a hard solid composition involves the formation of a so-called Sorel cement (sometimes written as Sorel's cement, and which is also known as magnesium oxychloride cement). It is made by mixing a saturated solution of magnesium chloride with magnesium oxide powder. The resulting paste sets with time to a hard marble like mass. It has the chemical composition represented by $MgCl_2.5MgO.H_20$. Sorel cement is used *inter alia* as dental filling, for the making of floor coverings and laboratory work places, for the preparation of magnesia compounds and in the lubrication of cotton threads for spinning. It is further known that Sorel cement may be mixed with sawdust or cork waste to produce a weatherproof wood like material called xitolite.

The applicant is not aware of any suggestion to use a Sorel cement as a carrier for a pharmaceutically active substance in a slow release preparation.

The reaction to produce Sorel cement is as follows:

$MgCl_2.6H_20 + 5MgO \rightarrow MgCl_2.5MgO.H_20 + 5H_20.$

The stoichiometry of this reaction indicates that the ideal mass ratio of $MgCl_2.6H_20$: MgO is 202 : 200, that is equal masses for all practical purposes. However in the present application for the entrapment of hygroscopic substances in a Sorel cement, it is preferable to use these ingredients in a ratio which presents an excess of MgO, i.e. preferably in a mass ratio of 0,99 $MgCl_2.6H_20$ to 1,25 MgO.

GENERAL DESCRIPTION OF THE INVENTION:

It has now unexpectedly been found that pharmaceutically active substances, such as the L-carnitine base was capable of being "dried" out by being incorporated into a Sorel cement and that it was acceptably stable in that form in the sense that it did not attract water during subsequent handling, such as during encapsulation.

It was also unexpectedly found that the L-carnitine so entrapped in the solid Sorel cement was released from the solid composition when taken into the body by being given orally, even though the compound, while entrapped in the solid composition, was insoluble in ordinary water.

It was also unexpectedly found that the solid composition released the L-carnitine over time and that this was thus suitable as a slow release composition or carrier medium.

It was further unexpectedly found that that a range of solid, particularly hygroscopic solid substances, as well as liquid substances which contain water such as the alcohols and in particular ethyl alcohol could be "dried" out and formulated into a solid composition by this method.

It was also unexpectedly found that gasses which are soluble in water, or in water containing liquids, could be trapped in Sorel cement to be released in the stomach upon being administered orally in the solid dosage form in issue.

Accordingly, the present invention provides a solid dosage form of a pharmaceutically active substance comprising a magnesium oxychloride cement (also known as Sorel cement) in which the pharmaceutically active substance is entrapped.

The solid dosage form may be a powder packed in a capsule.

Alternatively it may be in a compressed tablet form.

The magnesium oxychloride cement of the present invention is preferably made up by mixing a clear magnesium chloride solution containing the pharmaceutically active substance with magnesium oxide powder to form a paste which is then allowed to set over time into a solid composition, which composition is then crushed and milled to the desired fineness.

The pharmaceutically active ingredient is preferably a solid substance selected from the group consisting of L-carnitine, pantothenic acid, pyruvate and combinations thereof.

The pharmaceutically active ingredient may alternatively be a liquid substance such as ethyl alcohol (ethanol).

The pharmaceutically active substance may further alternatively be a gaseous substance which is soluble in water, such as, for example, nitrous oxide.

Without wishing to be bound by this theory, it is the applicant's view that since L-carnitine base is a polar molecule, this polarity attracts a lot of water and is the reason for its extreme hygroscopicity. The molecular water of the L-carnitine base is believed to be taken up during the magnesia (Sorel) cement reaction and both the molecular water and the L-carnitine base is solidified in the cement.

This is also believed to apply in the case of ethanol alone or in combination of L-carnitine with magnesium chloride and magnesium oxide. Both the ethanol and L-carnitine base is molecularly dehydrated and solidified by the reaction of the magnesium cement. Ethanol on its own is also dehydrated in this manner.

Any chemical compound with molecular water may accordingly be dehydrated on a molecular level and be solidified in the manner disclosed herein.

A gas which is soluble in water or in a water containing liquid, may also be entrapped in a solid composition in this manner. The gas may be nitrous oxide. A solution containing water and magnesium chloride may thus be saturated with nitrous oxide. This solution may then be used to make the magnesium (Sorel) cement. The nitrous oxide still present in the water would be entrapped in the solidified cement, and could then be grounded down into a powder to be encapsulated. The entrapped nitrous oxide would only be released once the compound reaches the stomach and is digested by the stomach acid.

It is further part of the applicant's non-binding theory that the mechanism of the process whereby the hydrochloric acid dissolves the composition is as follows:

Two hydrochloric acid molecules reacts with a magnesium oxide molecule to form magnesium chloride and water which in turn is utilized to form magnesium hydrochloride hexahydrate. Water would be taken from the immediate surroundings and the dehydration of the compound would be reversed. The slow release effect of the compound would depend on what the size of the molecule is e.g. $MgCl_2.3MgO.3H_2O$, would take a longer time to dissolve than $MgCl_2.2MgO.4H_20$. The active molecule such as L-carnitine or alcohol or nitrous oxide would be release at the rate at which the dominant molecules of the magnesia cement would be dissolved.

By mixing the compound for a longer period of time more of the $MgCl_2.4MgO.2H_20$ molecules would be present in the compound. The lesser time the compound is mixed the more of the $MgCl_2.3MgO.3H_20$ molecules would be present.

It may also be possible for the molecules to be absorbed as a unit e.g. $MgCl_2.4MgO.2H_20$. The concentrations would be too low to be detected in the serum. A study that was done found that there was increased L-carnitine excretion in the urine at 24 and 36 hours after a bolus dosage of 800 mg in

the composition. The most probable way that this could have been accomplished was that the molecules were absorbed intact and then slowly dissolved in the blood stream.

DESCRIPTION OF PREFERRED FORMULATION AND METHOD OF PRODUCTION:

A quantity representing 0,22 parts by mass of L-carnitine is dissolved in 0,23 parts by mass distilled water. This process must be completed and the resulting solution should be clear before 0,55 parts by mass of magnesium chloride hexahydrate is dissolved in the solution. This process should also be complete and the resulting solution should be clear.

A quantity representing 0,25 parts by mass of magnesium oxide is placed in an open powerful mixer after screening the powder through a sieve. A quantity representing 0,36 parts by mass of the magnesium chloride/L-carnitine/distilled water solution prepared as described above is added to the magnesium oxide while being mixed.

The mixture is initially dry when mixed and becomes a paste after approximately 15 - 20 minutes of mixing.

As soon as the firm paste is formed it is placed in a closed plastic container with a removable lid.

There is a rapid increase of temperature of the paste after 20 - 30 minutes to about 80°C. This reaction takes up to five minutes after which the paste is

set into a hard solid with a mass loss of approximately 5%. A great deal of steam is generated by this reaction and it pushes the lid from the container. Thereafter the dry composition is crushed, for example by means of a finger crusher to 5 mm size, then reduced to 1 mm size, for example by means of a hammer mill, and then reduced to sub-60 micrometer, for example by means of a pindisc mill.

This powder is then fine enough to be encapsulated in a hard gelatine capsule of 769 mg which would contain 254 mg magnesium chloride and 100 mg L-carnitine.

The presence of L-carnitine in the powdery composition could be detected at a mass to charge ratio (m/e) of 161 on a FAB-MS (Fast atomic bombardment mass spectrophotometer). The detection of the L-carnitine was only possible after the compound was treated with a weak solution of methanolic hydrochloride.

This compound needs hydrochloric acid to be dissolved. This is why it would only be dissolved for absorption in the body once it comes in contact with the hydrochloride acid in the stomach.

An analysis of the compound showed other peaks at mass to charge ratio of 244 and 266 this fits in with the following molecules $MgCl_2.2MgO.4H_20$

having a value of 246-2=244, and $MgCl_2.3MgO.3H_20$ having a value of 268 - 2 = 266.

This indicates that different cement molecules were present in the compound. In the stomach these would take different times to dissolve and thus having a slow release effect to release the active molecule such as L-carnitine. It is believed that the following molecules could be present in the Sorel cement composition.

1	$MgCl_2.5MgO.H_20$	amu = 312
2	$MgCl_2.4MgO.2H_20$	amu = 290
3	$MgCl_2.3MgO.3H_20$	amu = 268
4	$MgCl_2.2MgO.4H_20$	amu = 246
5	$MgCl_2.MgO.5H_20$	amu = 224

THE PHARMACEUTICAL APPLICATIONS FOR THE PRODUCTION AND APPLICATION OF THE DIFFERENT COMPOUNDS:

1. **Magnesium chloride / L-carnitine slow release**

A composition comprising dry magnesium chloride and L-carnitine in a hard gelatine capsule is unique. It releases L-carnitine over time for absorption through the stomach and intestine wall when taken orally.

The recommended dosage is one capsule twice a day or 2 capsules in the morning. The indication would be for all conditions requiring supplementary L-carnitine and magnesium administration. This copmposition could also be used to increase the HDL function of cholesterol.

2. **Magnesium chloride / L-carnitine / alcohol slow release**

One capsule containing 254 mg magnesium chloride, 100 mg L-carnitine and 70 mg Ethanol may be produced in the manner as described above. A mass representing 0,22 parts L-carnitine is dissolved in a mass representing 0,23 parts of 86% ethanol. A mass representing 0,55 parts magnesium chloride hexahydrate is added after the first components are dissolved completely.

A mass representing 0,36 parts of this clear solution is added to a mass representing 0,25 parts magnesium oxide while being mixed. The resulting paste is placed in a closed container to contain the evaporation of ethanol. There is no significant increase in temperature after 20 - 30 minutes and the compound takes 2 - 3 days to dry out and to set to a solid mass.

This compound could also be made without the L-carnitine and by using the same mass ratios for the alcohol, magnesium chloride and magnesium oxide a dry slow release compound could be made with magnesia cement and ethanol. The compounds with alcohol could then be used to treat people with alcohol abuse problems seeing that most of those people have a magnesium and L-carnitine deficiency and that this, together with the 70 mg alcohol per capsule, would enable them to stop their drinking habits. The recommended dosage is 2 capsules twice a day for one-week, then 2 capsules per day for 3 months and then 2 placebo capsules per day of the capsules without the alcohol.

This compound could also be used to increase the HDL fraction of cholesterol. It is known the moderate intake of ethanol, magnesium supplement and L-carnitine individually increases HDL cholesterol. This invention provides the means to produce a product that contains all the above mentioned in a single dry composition to be taken orally.

3. **Magnesium chloride / L-carnitine / nitrous oxide slow release**

A mass representing 0,22 parts L-carnitine is dissolved in a mass representing 0,23 parts distilled water. A mass representing 0,55

parts magnesium chloride hexahydrate is added to dissolve completely. This solution is saturated by nitrous oxide gas by using pressure. A mass representing 0,36 parts of this solution is added to a mass ratio of 0,25 magnesium oxide and mixed. The resulting paste is placed in a closed container to dry while preventing the escape of the gas. The dried composition is then grounded down.

An indication for use of this compound would be for the oral treatment of HIV infection, viral infections, gout, psoriasis, cancer, rheumatism, hypercholesterol, alcoholism and osteoporosis.

The compound could also be used for its anti-inflammatory action against viral infections in animals and birds including ostriches. It could also be used as an anti-inflammatory in allergic reactions or in cases of an overactive immune system.

4. **Magnesium chloride/nitric oxide slow release**

A mass representing 0,55 parts of magnesium chloride hexahydrate is dissolved completely in a mass representing 0,23 parts distilled water. This solution is saturated by nitric oxide gas by making use of pressure. A mass representing 0,36 parts of this solution is added to a mass representing 0,25 parts magnesium oxide. The resulting paste

is placed in a closed plastic container to dry. The dried compound is then grounded down. The indications of this compound is the same as the magnesium L-carnitine/nitrous oxide compound.

5. **Magnesium chloride / L-carnitine / nitric oxide slow release and Magnesium chloride/nitrous oxide slow release**

This process and ratios is the same as the process for nitrous and nitric oxide compositions numbers three and four above. Care must be taken however, particularly in the case of nitric acid formulations to use deoxygenated water and the mixing should take place in an enclosed environment to minimize the inclusion of oxygen in the compound so that nitric acid formation could be minimized or excluded.

6. **Magnesium / pantothenic acid slow release**

A mass representing 0,22 parts pantetonate is dissolved in a mass representing 0,23 parts distilled water. A mass representing 0,55 parts magnesium chloride hexahydrate is added to dissolve completely. A mass representing 0,36 parts of this solution is mixed with a solution of a mass representing 0,25 parts magnesium oxide. The resulting paste is placed in a container to dry. The dried

compound is then grounded down and encapsulated. It is used in any application wherein the supplementation of diet by pantetonate is indicated.

7. **General molecular dehydration of hygroscopic substances**

The mass representing 0,22 parts of the substance to be "dehydrated" and which is to be dissolved in distilled water with a mass representing 0,23 parts of H_2O is to be used for the total of one or more of the substances to be added. If necessary the distilled water could be rendered more alkaline by adding a mass representing 0,006 sodium hydroxide. In this regard it is desirable to adjust the pH of the aqueous solution of the substance to be entrapped to a value below 7, and preferably to a value between 7 and 9 before addition of the magnesium chloride thereto. A mass representing 0,55 parts magnesium chloride hexahydrate is then used to complete the solution. A mass representing 0,36 parts of this solution is thereupon added to a mass representing 0,25 parts of dry powdery Magnesium Oxide as a general rule, which rule may require refinement in certain circumstances.

Countless variations of the invention may be devised without departing from the spirit of the invention which may also in particular be applied in the formulation of compositions containing any of the following ingredients:

acetylcarnitine; creatine and derivatives; Vitamin F oil; ostrich oil; fat soluble vitamins such as Vitamin A and derivatives thereof or Vitamin E (dl-tocopherol); steroids; hormones, e.g. estrogen and testosterone; plant extracts including oils, water soluble fractions and ethanolic extractions; nicotinamide adenine dinucleotide (NAD); and fluorine gases such as halothane and the like.

CLAIMS:

1. A solid dosage form of a pharmaceutically active substance comprising a magnesium oxychloride cement (also known as a Sorel cement) in which the pharmaceutically active substance is entrapped.

2. The solid dosage form of claim 1 in which the cement is in the form of a powder packed in a capsule.

3. The solid dosage form of claim 1 in which the cement is in a compressed tablet form.

4. The solid dosage form of claim 1 in which the magnesium oxychloride cement is made up by mixing a clear magnesium chloride solution containing the pharmaceutically active substance with magnesium oxide powder to form a paste which is then allowed to set over time into a solid composition which composition is then optionally crushed and milled to the desired fineness.

5. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active ingredient is a solid substance selected from the group consisting of L-carnitine, pantothenic acid, pyruvate and combinations thereof.

6. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active ingredient is a liquid substance such as ethyl alcohol (ethanol).

7. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active substance is a gaseous substance which is soluble in water, such as, for example, nitrous oxide.

8. A method of producing a solid dosage form of a pharmaceutically active compound comprising the steps of forming a clear basic aqueous solution of the compound, dissolving magnesium chloride hexahydrate into that solution and using the resultant solution to form magnesium oxide powder into a paste, allowing the paste to set into a solid composition and, if desired, grinding the set composition into a powder.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 123 693 A (NAT RES DEV) 8 February 1984 (1984-02-08) page 3, line 34 -page 4, line 14 page 5 -page 6; example 2 claim 1	1,3,4
X	EP 0 357 327 A (NAT RES DEV) 7 March 1990 (1990-03-07) page 2, line 23 - line 34 page 3, line 64 -page 4, line 2 page 4, line 64 - line 65 claim 1	1,3,4
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 123 693 A (NAT RES DEV) 8 February 1984 (1984-02-08) page 3, line 34 -page 4, line 14 page 5 -page 6; example 2 claim 1	1,3,4
X	EP 0 357 327 A (NAT RES DEV) 7 March 1990 (1990-03-07) page 2, line 23 - line 34 page 3, line 64 -page 4, line 2 page 4, line 64 - line 65 claim 1	1,3,4
A	US 5 273 547 A (REIDIES ARNO H) 28 December 1993 (1993-12-28) the whole document	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2001	15/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muller, S

1

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2123693 A	08-02-1984	GB 2123690 A	08-02-1984
		AU 566878 B	05-11-1987
		AU 1699583 A	26-01-1984
		CA 1228296 A	20-10-1987
		DE 3326168 A	26-01-1984
		FR 2530467 A	27-01-1984
		JP 1688581 C	11-08-1992
		JP 3042872 B	28-06-1991
		JP 59039259 A	03-03-1984
		NZ 204861 A	08-10-1986
		US 4880628 A	14-11-1989
		US 4661339 A	28-04-1987
		ZA 8308113 A	24-12-1984
EP 0357327 A	07-03-1990	GB 2222082 A	28-02-1990
US 5273547 A	28-12-1993	US 4961751 A	09-10-1990
		US 5152804 A	06-10-1992
		AU 3372889 A	02-11-1989
		DK 209589 A	30-10-1989
		EP 0339674 A	02-11-1989
		FI 892056 A	30-10-1989
		JP 1321978 A	27-12-1989
		KR 9201017 B	01-02-1992
		NO 891759 A	30-10-1989
		US 5261924 A	16-11-1993

PATENT COOPERATION TREATY

RECD 11 DEC 2001

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P20097PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ZA00/00180	29/09/2000	29/09/1999
International Patent Classification (IPC) or national classification and IPC		
A61K9/20		
Applicant		
H J DAVIS FINE CHEMICALS CC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☐ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/04/2001	07.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Muller, I Telephone No. +49 89 2399 8716

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ZA00/00180

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1,2,5-19	as originally filed	
3,4	with telefax of	26/11/2001

Claims, No.:

1-7	with telefax of	26/11/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,5-8
	No:	Claims	1,3,4
Inventive step (IS)	Yes:	Claims	5-7
	No:	Claims	1-4,8
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item I

Basis of the report

The amendments filed with telefax dated 26.11.2001 cannot be taken into consideration in the present opinion as the requirement set forth by Article 34(2)(b) PCT has not been met. The subject-matter of the following claims goes beyond the disclosure in the application as originally filed:

The independent claim 1 directed to a solid dosage form, as well as the dependent claim 7 referring to the independent claim 6 directed to a method of producing a solid dosage form encompass combinations of pharmaceutically active substances for which neither basis can be found in the specification nor in the claims as originally filed.

Claims 5 to 7 as originally filed, each referring to particular sort active substances (in solid, liquid, respectively gaseous form) are dependent on claims 1-4. The specification solely defines as particular combinations on pages 13-19 L-carnitine/ethanol (p. 14); L-carnitine/nitrous oxide (p. 15) and L-carnitine/nitric oxide (p. 17).

Consequently, the present international preliminary examination report is drawn up on the basis of the claims 1-8 as originally filed.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:
   D1: GB-A-2 123 693 (NAT RES DEV) 8 February 1984 (1984-02-08)
   D2: EP-A-0 357 327 (NAT RES DEV) 7 March 1990 (1990-03-07).

2. Novelty (Article 33(2) PCT)

2.1 The subject-matter of claim 1 is anticipated by the prior art as follows:
D1 discloses in example 2 a cylindrical pharmaceutical device (solid dosage form) comprising magnesium oxychloride cement entrapping magnesium as active substance, which is prepared by mixing a magnesium chloride solution with magnesium oxide powder ../..
Even though D2 appears to be directed to sustained release devices formed by a reaction cement of magnesium oxide base plus magnesium sulphate (see claims, page 4, l. 25-52), this document discloses at page 4, l. 64-65 a dosage form

comprising magnesium oxychloride cement and as active agent amprolium, which is novelty destroying for the subject-matter of present claim 1.

2.2 Further, the dosage forms of D1 (p. 4, l. 11-15) and D2 (p. 4, l. 1-2) may be a tablet, anticipating the subject-matter of present dependent claim 3.
In example 2 of D1, the cylindrical device is made by mixing a magnesium chloride solution containing the active substance (magnesium) with the magnesium oxide powder. The formation of a paste as well as setting into a solid is implicit from the preparation of a cylindrical device. Hence, the subject-matter of the dependent claim 4 is considered lacking novelty over D1.

2.3 None of the documents cited in the international search report discloses solid dosage forms comprising a magnesium oxychloride cement and a pharmaceutically active substance such as defined in present dependent claims 5-7.
Hence, the subject-matter of each of the claims 5, 6 and 7, referring to the independent claim 1, is considered satisfying the requirement of novelty.

2.4 None of the documents cited in the international search report further discloses a method of producing a solid dosage form comprising the steps of forming an aqueous solution of a pharmaceutically active compound, then dissolving magnesium chloride hexahydrate in that solution.
Hence, in view of the prior art cited in the international search report, the subject-matter of the independent claim 8, is considered satisfying the requirement of Article 33(2) PCT.

3. Inventive Step (Article 33(3) PCT)

3.1 The problem underlying the independent claim 8 is understood as lying in the provision of providing a method for preparing a sustained release device comprising magnesium oxychioride cement and a pharmaceutically active compound.
The expression 'clear basic solution' is not considered as having a precise meaning in the present case. At no place of the specification, reference is made to providing a solution of pharmaceutically active compound with a particular pH.

The term basic may hence also be understood as meaning that the basis of the method of preparation is a clear aqueous solution of active compound.
D1 discloses the preparation of magnesium oxychloride cement by mixing magnesium oxide powder with an aqueous magnesium chloride solution (see example 2), in order to prepare sustained release cylindrical devices comprising as pharmaceutically active agent magnesium and thus, represents the closest prior art.
In view of the technical teaching of D1 it is considered common procedure of the person skilled in the technical field, to add any of the substances with medicinal effect disclosed at page 3, l. 57 to page 4, l. 3 which are envisaged to be included into said devices, before the formation of the cement, i.e. before addition of the magnesium oxide powder to the aqueous magnesium chloride and moulding into a solid cylindrical shape. Moreover, neither formation of a 'clear' aqueous solution of a pharmaceutically agent in general appears to lead to a new and non-obvious effect of the method defined in claim 8 over the cited prior art.

3.2 Neither a new and non-obvious effect is apparent for the subject-matter of the dependent claim 2, referring to claim 1, differing from D1 solely in that magnesium oxychloride cement is packed in a capsule.

3.3 The problem underlying each of the dependent claims 5, 6 and 7 is considered as lying in the provision of providing a solid delivery device particularly suited for the administration of the active compounds defined in afore-said claims.
In view of the technical teaching of D1, neither hint nor suggestion is apparent that would point towards particularly choosing magnesium oxychloride cement as delivery device in order to 'dry out' hygroscopic solid and liquid active substances or entrap in this cement particular gaseous substances, as defined in present claims 5, 6 and 7, in order to provide solid sustained delivery devices for administration of the said active compounds.

Hence, the subject-matter of each of the dependent claims 5, 6 and 7, depending on claim 1 appears to meet the requirement of Article 33(3) PCT.

4. The subject-matter of the present claims 1-7 is applicable in the pharmaceutic industry.

has accordingly long been considered impossible to administrate them separately, let alone together in the most desirable dosage form, namely as a dry, solid preparation, e.g. in tablet, capsule or granule form. They are presently being administrated together as a liquid compound. This liquid formulation is not generally considered to be user friendly, and hence conducive to patient compliance, as it has an unpleasant taste and has to be diluted in other liquids.

OBJECTS OF THE INVENTION:

To address the above problems, the present invention proposes, and is based upon, the hitherto unknown utilization of a method which, although known as such as a method of solidifying magnesium chloride hexahydrate, has, as far as the applicant is aware, not yet been suggested for use in the manner proposed herein for the preparation of the slow- or sustained release preparations of any one of the wide range of pharmaceutically beneficial products, including, but not limited to L-carnitine, which may be incorporated into the solid composition as proposed by the present invention.

It is accordingly an object of the present invention to provide a solid, slow release dosage form of a pharmaceutically active substance or combination of substances, and specifically, though not exclusively, of a substance or combination of substances which is hygroscopic, or which is a liquid which

contains or is soluble in water, such as, for example, the compound L-carnitine, alcohol and nitrous oxide gas.

PRIOR ART TO THE INVENTION:

The aforementioned known method of converting magnesium chloride into a hard solid composition involves the formation of a so-called Sorel cement (sometimes written as Sorel's cement, and which is also known as magnesium oxychloride cement). It is made by mixing a saturated solution of magnesium chloride with magnesium oxide powder. The resulting paste sets with time to a hard marble like mass. It has the chemical composition represented by $MgCl_2.5MgO.H_20$. Sorel cement is used *inter alia* as dental filling, for the making of floor coverings and laboratory work places, for the preparation of magnesia compounds and in the lubrication of cotton threads for spinning. It is further known that Sorel cement may be mixed with sawdust or cork waste to produce a weatherproof wood like material called xitolite.

The applicant is not aware of any suggestion to use a Sorel cement as a carrier for a pharmaceutically active substance in a slow release preparation.

The reaction to produce Sorel cement is as follows:

$MgCl_2.6H_20 + 5MgO \rightarrow MgCl_2.5MgO.H_20 + 5H_20.$

CLAIMS:

1. A solid dosage form of a pharmaceutically active substance comprising a magnesium oxychloride cement (also known as a Sorel cement) in which the pharmaceutically active substance is entrapped.

2. The solid dosage form of claim 1 in which the cement is in the form of a powder packed in a capsule.

3. The solid dosage form of claim 1 in which the cement is in a compressed tablet form.

4. The solid dosage form of claim 1 in which the magnesium oxychloride cement is made up by mixing a clear magnesium chloride solution containing the pharmaceutically active substance with magnesium oxide powder to form a paste which is then allowed to set over time into a solid composition which composition is then optionally crushed and milled to the desired fineness.

5. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active ingredient is a solid substance selected from the group consisting of L-carnitine, pantothenic acid, pyruvate and combinations thereof.

6. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active ingredient is a liquid substance such as ethyl alcohol (ethanol).

7. The solid dosage form of any one of claims 1 to 4 wherein the pharmaceutically active substance is a gaseous substance which is soluble in water, such as, for example, nitrous oxide.

8. A method of producing a solid dosage form of a pharmaceutically active compound comprising the steps of forming a clear basic aqueous solution of the compound, dissolving magnesium chloride hexahydrate into that solution and using the resultant solution to form magnesium oxide powder into a paste, allowing the paste to set into a solid composition and, if desired, grinding the set composition into a powder.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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D.M. KISCH Inc.
P O. Box 781218
SANDTON 2146
AFRIQUE DU SUD

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	07.12.2001
Applicant's or agent's file reference: P20097PC00	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ZA00/00180	29/09/2000	29/09/1999

Applicant: H J DAVIS FINE CHEMICALS CC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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